ORIGINAL ARTICLE

Induction therapy with twice-daily interferon-beta does not improve the therapeutic efficacy of consensus interferon monotherapy for chronic hepatitis C

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Abstract. We examined therapeutic superiority of induction therapy with twice-daily IFN-β (3X2=6 million units/day) onto 6-months consensus interferon monotherapy for chronic hepatitis C. Patients were randomly assigned to monotherapy without (group I, n=16) and with induction therapy (group II, n=12). The mean age of group II was older than that of group I, and other baseline condition was not statistically significant. Sustained virological response (SVR) rates of group I and II were 81.3% (13/16) and 58.3% (7/12), respectively (p=0.365). SVR rates in patients with genotype 1b were 66.7% (4/6) and 0% (0/2, because of drop-out), and those with high viral load were 70% (7/10) and 75% (6/8) in group I and II, respectively (p=1.000). Drop-out rates during therapy were 6.3% (1/16) and 33.3% (4/12) in group I and II, respectively (p=0.176). Age less than 50 years was the only independent factor that was shown by multivariate logistic model analysis to be associated with a sustained virological response. Although randomization failed to produce and equal age distribution in the two groups in this study, our results suggest that induction therapy with twice-daily IFN-β has no beneficial effect on the efficacy of monotherapy with consensus interferon, probably because of the higher drop-out rates and incidence of adverse reactions with induction therapy. (Keio J Med 55 (3): 111–117, September 2006)

Key words: consensus interferon, interferon-beta, induction therapy, monotherapy

Introduction

The worldwide prevalence of hepatitis C virus (HCV) infection is estimated at 170 million people, and the natural history of this infectious disease involves progression to chronic liver failure or liver cirrhosis with complications such as hepatocellular carcinoma.[1] Interferon (IFN) therapy has been approved for HCV treatment in Japan since 1993 and treatment has since been improved by the development of several new types of IFN. Recently, combination treatment with pegylated IFN (Peg-IFN) and ribavirin (RBV) for at least one year has been recommended for patients with HCV genotype 1b and a high viral load (>100 KIU/mL).[2,3] This group of patients is thought to be difficult to treat; they show sustained viral response (SVR) rates of less than 10% following 6-month IFN monotherapy, although this has recently been improved to 50% with 1-year Peg-IFN plus RBV combination therapy.

Consensus IFN (CIFN), also referred to as IFN al-

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facon-1, is a recently developed recombinant form of IFN. This type of recombinant IFN was produced by assigning the most frequently observed amino acid in each position (consensus amino acid in a position) after scanning the sequences of several known IFN-α subtypes.[4] CIFN has demonstrated higher antiviral effects *in vitro* and *in vivo*, and less adverse reactions *in vivo* than natural IFN-α, recombinant IFN-α2a, or IFN-α2b.[5,6] The results of previous studies in Japan have demonstrated that CIFN at a dose of 18 MU is effective and tolerable in patients with chronic HCV and a high viral load.[7]

On the other hand, twice-daily IFN-β administration was reported to result in a higher response rate than once-daily administration by compensating for the compounds short half-life. Several studies suggested that IFN-β triggers biological responses distinct from those of IFN-α and through different downstream signals, although the same receptor type should be utilized by both IFN-α and-β. Twice-daily administration of IFN-β decreases HCV RNA more than does once-daily dosing, especially during the first 14 days of treatment.[8,9]

On the basis of these findings, we tested combination treatment for chronic hepatitis C with CIFN and induction therapy with twice-daily IFN-β. We analyzed the efficacy and tolerability of this induction therapy in a multicenter, randomized, open-trial.

Patients and Methods

Patients

This study was approved by the ethical committee of the Keio University, School of Medicine, and the University Hospital. The affiliated hospitals of Keio University participated in this study, and the protocol was approved by the ethical committee of each hospital. Patients with chronic hepatitis C who visited these hospitals from March 2002 to September 2003 were enrolled in this study. Patients having HCV RNA levels more than 500 KIU/mL were excluded from the study, because CIFN monotherapy has been reported to have little efficacy on this group of patients. Hepatitis B virus – and human immunodeficiency virus–positive patients, those whose daily alcohol consumption exceeded 60 g, and those with other types of liver diseases were excluded. Most patients received a liver needle biopsy before having treatment, and histological assessment was performed according to the New Inuyama Classification, which is a standard diagnostic criterion in Japan. HCV RNA levels were examined using an AmpiCor GT-HCV Monitor Version 2.0 (Roche Molecular Systems, Pleasanton, CA, USA) and HCV serotypes were examined by the enzyme immunoassay for HCV grouping. Serum transaminase levels, blood cell counts, and other biochemical measurements were sequentially examined. Adverse reactions were monitored by careful interview and medical examination throughout the study. Because fever and other influenza-like symptoms are frequent side effects, non-steroid anti-inflammatory drugs were prescribed for all patients and were taken if the symptoms occurred.

Treatment

At the start of therapy, the Japanese Ministry of Labor and Welfare had only approved 6-month IFN therapy for chronic hepatitis C, and Peg-IFN had been approved. RBV was approved in December 2001. Patients having HCV viremia and suffered from histologically proven chronic hepatitis C were enrolled. Informed consent of participation to this study was obtained from each patient with a written document and the signature. Thirteen hospitals, Keio University hospital (4), Tachikawa Hospital (5), TEPCO Hospital (4), Tokyo Dental Collage Ichikawa General Hospital (3), Eiju Hospital (2), Saitama Social Institute Hospital (2), Minami-Tama Hospital (2), Fussa Hospital (1), Keiyu Hospital (1), Kitasato Institute Hospital (1), Nihon Kohkan Hospital (1), Tokyo Medical Center (1), Tokyo Metropolitan Ohtsuka Hospital (1) (The number of patients enrolled) were participated in this study. Patients were randomly assigned to two treatment groups; group I, receiving 18 MU/day CIFN (Advaferon®, Amgen Inc. Thousand Oaks, CA, USA) subcutaneously daily for 2 weeks and three times a week for 22 weeks, and group II, receiving 3 MU of twice-daily (totally 6 MU/day) IFN-β (Feron®, Toray, Tokyo, Japan) intravenously for 2 weeks (induction) and then 18 MU/day CIFN three times a week for 22 weeks. Randomization was performed by an envelope methods. The treatment protocol was decided after the enrollment was assigned to the group at the central office of this study located at the Keio University. The dose was reduced to 12 MU/day if side effects such as decreased blood cell counts appeared. When side effect occurred during the first 2 weeks of treatment in group II, the dose of IFN-β was reduced to 3 MU once-daily. SVR was defined as the absence of serum HCV RNA from the end of treatment until 6 months post-treatment. The treatment was stopped when a patient declined having further treatment because of adverse effects, such as high fever, itchy eruption, severe fatigue, alopecia, and so on. When the physician found severe adverse reactions, such as proteinuria, leucopenia (<2,000/mm^3), low platelet counts (<50,000/mm^3), elevation of ALT levels (>500 IU/L), and depressive state, the treatment was stopped with an agreement.

Statistics

Treatment outcome was analyzed on an intention-to-

Table 1 Baseline distribution of various clinical factors of the patients according to treatment regimens

Baseline factor	Group I	Group II	p value
Age[a] (mean±SD)	45.8±10.0	56.2±10.3	0.0128
Habitual Drinking[b]	11 (68.8%)	8 (66.7%)	1.0000
Past IFN therapy[b] (+)	9 (56.3%)	9 (75.0%)	0.5312
Genotype[b] 1b	6 (37.5%)	2 (16.7%)	0.5149
2a/2b	10 (62.5%)	9 (75.0%)	
Unknown	0	1 (8.3%)	
HCV RNA[b] <100 KIU/mL	6 (37.5%)	4 (33.3%)	1.0000
≥100 KIU/mL	10 (62.5%)	8 (66.7%)	
Liver Histology[c]			
F stage F1	7 (58.4%)	6 (54.6%)	0.8890
F2	4 (33.3%)	4 (36.4%)	
F3	1 (8.3%)	1 (9.0%)	
Unknown	4	1	
A grade A1	4 (33.3%)	4 (36.4%)	0.9377
A2	7 (58.4%)	7 (63.4%)	
A3	1 (8.3%)	0	
Unknown	4	1	
Biochemistry[a] (mean)			
AST (IU/L)	59.6	70.3	0.4564
ALT (IU/L)	80. 6	118.0	0.1337
γGTP (IU/L)	62.8	51.4	0.5026
ALB (g/dL)	4.30	4.17	0.4275
Hb (g/dL)	14.6	13.9	0.3301
WBC (/μL)	5801	5785	0.9784
PLT (10^4/μL)	19.7	19.1	0.8055

ALB, albumin; PLT, platelet counts; [a]analyzed by t-test for continuous factors, [b]analyzed by Chi-square test for binary factors, [c]analyzed by Wilcoxon test for ordinal factors

treat basis and we also analyzed on a per-protocol basis. Patients' background was analyzed by Student t-test, Wilcoxon test, and chi-square test. Differences in efficacy, adverse reactions, and other parameters between treatment groups were analyzed by Fisher's exact test, Mann-Whitney U test and chi-square test. Predictive factors for obtaining SVR were analyzed using a logistic model among factors such as treatment regimen (group I or II), age (<50 or ≥50), gender (male or female), habitual alcohol consumption (+ or -), HCV genotype (1b or 2a/2b), baseline viral load (<100 KIU/mL or ≥ 100 KIU/Ml), F stage (F1 or F2/3), and A grade (A1 or A2/3).

Table 2 Sustained virological response rates and clinical factors according to treatment groups

Factors		Group I	Group II	p value
All cases[a]		81.3% (13/16)	58.3% (7/12)	0.3651
Age[a]	<50	100% (9/9)	75.0% (3/4)	0.6645
	≥50	57.1% (4/7)	50% (4/8)	1.0000
Gender[a]	Male	72.7% (8/11)	50.0% (4/8)	0.5945
	Female	100% (5/5)	75.0% (3/4)	0.9056
Drinking habit[a]	−	80.0% (8/10)	54.6% (6/11)	0.4399
	+	83.3% (5/6)	100% (1/1)	1.0000
Past IFN[a]	−	100% (9/9)	55/6% (5/9)	0.0890
	+	57.1% (4/7)	66/7% (2/3)	1.0000
Genotype[a]	1b	66/7% (4/6)	0% (0/2)	0.4142
	2a/2b	90.0% (9/10)	66.7% (6/9)	0.4951
HCV RNA[a]	<100 KIU/mL	100% (6/6)	25.0% (1/4)	0.0671
	≥100 KIU/mL	70% (7/10)	75.0% (6/8)	1.0000
Liver histology[b]				
F stage	F1	85.7% (6/7)	50.0% (3/6)	0.4306
	F2	100% (4/4)	75.0% (3/4)	1.0000
	F3	100% (1/1))	100% (1/1)	
A grade	A1	100% (4/4)	3.3% (1/3)	0.2771
	A2	85.7% (6/7)	85.7% (6/7)	1.0000
	A3	100% (1/1)	0% (0/0)	

Statistical analysis was performed by [a]Chi-square test, [b]Wilcoxon test for ordinal factors.

Results

Patient backgrounds

The comparison of patient backgrounds is shown in Table 1. No statistical difference was found in gender, past blood transfusion, alcohol consumption, past IFN treatment, HCV genotypes, HCV RNA levels, liver histology, basal transaminase levels, other biochemical parameters, blood cell counts, positivity of anti-nuclear antibody, immunoglobulin levels, urine protein, and urine glucose. Age was the only factor that differed significantly; the mean age was greater in group II than in group I (56.2 vs 45.8 year old, p=0.013).

Virological response

SVR was achieved in 13 of 16 (81.3%) and 7 of 12 (58.3%) patients in Group I and II, respectively (p=NS). Serum HCV RNA disappeared 4 weeks after the start of

Table 3 Sustained biochemical response rates and clinical factors according to treatment groups

Factors		Group I	Group II	p value
All cases[a]		68.8% (11/16)	58.3% (7/12)	0.8644
Age[a]	<50	100% (9/9)	50.0% (2/4)	0.1407
	≥50	57.1% (2/7)	50% (5/8)	0.4264
Gender[a]	Male	63.6% (7/11)	62.5% (5/8)	1.0000
	Female	80.0% (4/5)	50.0% (2/4)	0.8125
Drinking habit[a]	−	70.0% (7/10)	54.5% (6/11)	0.7806
	+	66.7% (4/6)	100% (1/1)	1.0000
Past IFN[a]	−	77.8% (7/9)	55/6% (5/9)	0.6171
	+	57.1% (4/7)	66/7% (2/3)	1.0000
Genotype[a]	1b	83.3% (5/6)	0% (0/2)	0.6733
	2a/2b	80.0% (8/10)	33.3% (3/9)	0.8908
HCV RNA[a]	<100 KIU/mL	83.3% (5/6)	100% (4/4)	1.0000
	≥100 KIU/mL	60% (6/10)	37.5% (3/8)	0.6353
Liver histology[b]				
F stage	F1	85.7% (6/7)	66.7% (4/6)	0.8789
	F2	75.0% (3/4)	75.0% (3/4)	1.0000
	F3	100% (1/1))	0% (0/1)	
A grade	A1	100% (4/4)	100% (3/3)	
	A2	71.4% (5/7)	57.1% (4/7)	1.0000
	A3	100% (1/1)	0% (0/0)	

Statistical analysis was performed by [a]Chi-square test, [b]Wilcoxon test for ordinal factors

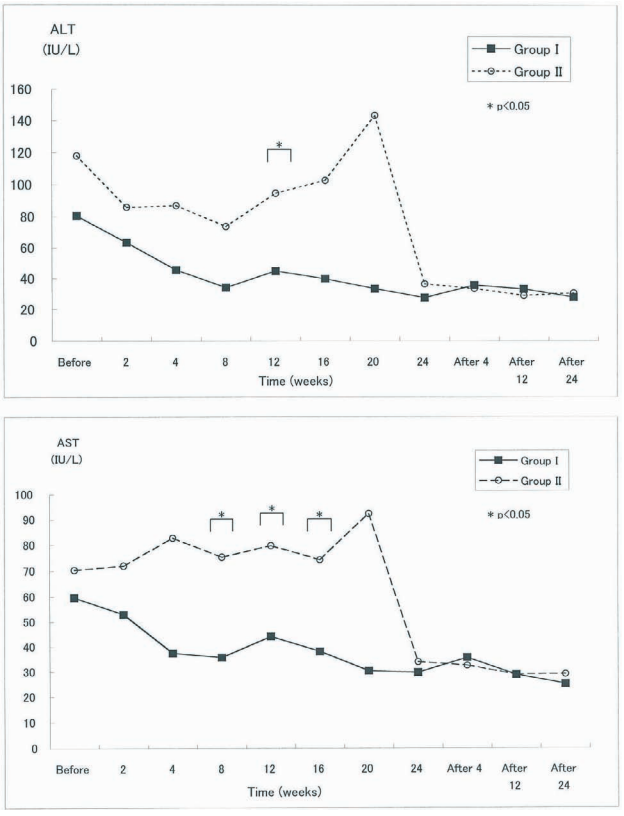

Fig. 1 Serum transaminase levels before, during, and after the therapy. Serum transaminase (AST and ALT) levels before, during and after treatment are shown sequentially according to treatment groups. The solid line indicates levels in group I and the dotted line indicates levels in group II. Asterisks indicate time points for which statistical significance ($p<0.05$) was found. Statistical significance was analyzed using student t-test by time.

therapy in 91.7% and 71.4% of patients in group I and II, respectively (p=NS). Several factors were analyzed in relation to treatment efficacy, and no significant difference in SVR rates between the two treatment regimens were found for any of these factors (Table 2). SVR was achieved in 6 of 6 (100%) patients with low HCV RNA levels (<100 KIU/mL) in group I, and only one patient was over 50 year old in 6 patients with low viral load (<100 KIU/mL). This one patient obtained SVR. On the other hand, all the 4 patients in the induction group (group II) having low viral load were over 50 year old, and only 1 of 4 (25%) in group II (p=NS) responded. In patients with genotype 2 (2a/2b), the response rate was high, and SVR was achieved in 9 of 10 (90.0%) and 6 of 9 (66.7%) patients in group I and II, respectively. SVR rates of patients with high viral load (>100 KIU/mL) were 70.0% (7/10) and 75.0% (6/8) in group I and II, respectively (p=NS). In patients with HCV genotype 1b, the response rate was 66.7% (4/6) in group I, and 2 patients in group II dropped out because of adverse reactions. In difficult-to-treat patients who had genotype 1b and high viral loads, SVR was obtained in 1 of 5 (20.0%) patients in group I and 0 of 2 (0%) in group II.

We found the same result of this intention-to-treat analysis with per-protocol analysis. SVR was achieved in 13 of 15 (86.7%) and 5 of 8 (62.5%) patients in Group I and II, respectively (NS). All patients under 50 year old (n=9 and 2 in group I and II, respectively) well responded to the therapy and obtained SVR, even in patients with genotype 1b (3 patients in group I). SVR was achieved in 7 of 12 patients over 50-year-old (6 in group I and 6 in group II). In group I, 4 of 6 patients (66.7%) obtained SVR and 3 of 6 patients (50%) obtained in group II.

Biochemical respones

Sustained biochemical response (SBR; serum transaminase levels are stable within normal range for more than 6 months after the end of therapy) was achieved in

Table 4 Contributing factors for achieving sustained virological response by multivariate analysis

Factors		Odds ratio	95% C.I.	p value
Regimen	group I	6.62	0.49－393.13	0.136
	group II	1.00		
Age	<50	14.99	0.98－1175.62	0.028
	≥50	1.00		
HCV genotype	1b	0.08	0.00－1.41	0.098
	2a/2b	1.00		

Statistical analysis was performed by logistic regression analysis using exact estimation.

Table 5 Adverse reactions

Reaction	Group I	Group II
General fatigue	4	3 (1)
Fever	3	4
Decrease in WBC	3	1
Eruption	2 (1)	2 (1)
Swelling of injection site	0	3 (1)
Depression	0	2 (1)
Proteinurea	0	1
Alopecia	0	1

Values in parentheses indicates the number of patients who stopped treatment because of side effects.; WBC, white blood cell counts

11 of 16 (68.8%) and 7 of 12 (58.3%) patients in group I and II, respectively (p=NS). There were no significant differences in SBR rates between treatment regimens for any of the clinical factors (Table 3). Serum transaminase levels (aspartate aminotransferase, AST; alanine aminotransferase, ALT) were monitored every 4 weeks until 24 weeks after cessation of therapy. Transaminase levels in group II patients were always higher than those of group I patients during treatment (Fig. 1) ALT levels at 12 weeks and AST levels at 8, 12 and 16 weeks were significantly higher in group II than in group I. These differences no longer existed after cessation of treatment.

Logistic regression analysis

Only age (p=0.038) was found to be a significant predictive factor for achieving SVR between these factors by univariate analysis. The predictive factor was also analyzed with "per-protocol" basis, and only age (p=0.037) was found to be significant.

To determine which factor contributed to obtaining SVR, a multivariate logistic model analysis was performed among–regimen, age and HCV genotype, because regimen and HCV genotype were factors with p-values less than <0.1 in the univariate analysis (Table 4). Only age was found to be statistically significant, and the odds ratio for younger patients (<50-year-old) was 2.71 (95% C.I. 0.98-1175.62). This factor, age, was similarly pointed-out when per-protocol analysis was applied (p=0.046).

Adverse reactions

Adverse reactions appeared in 9 of 16 (55.3%) and 12 of 12 (100%) patients in group I and II, respectively (Table 5). Treatment was discontinued in only 1 of 16 (6.3%) patients in group I and 4 of 12 (33.3%) in group II (p=NS) because of adverse reactions. Moderate decrease in blood cell counts was observed in 4 cases, and treatment was discontinued in 1 case. All side effects abated after cessation of therapy. One patient in group II dropped out because of eruption during the first two weeks when IFN-β was administered. Other three patients in group II dropped out after two weeks when CIFN was administered. Leukopenia, decrease in platelet counts, retinopathy and proteinuria have been more frequently reported in IFN-β treatment than in IFN-α treatment, but no patient dropped out by these side effects in this study.

Discussion

In the present study, we examined IFN monotherapy for 6 months, which was the standard therapy in Japan until December 2001. RBV, which is always administered with IFN, is a nucleoside analogue that facilitates the anti-viral efficacy of IFN, and was approved in December 2001 by the Japanese Ministry. Since then, IFN-α2b plus RBV combination therapy for 6 months became the standard therapy for difficult-to-treat patients.[10] At that time, the duration of IFN monotherapy was limited to 6 months, and the SVR rates reported in difficult-to-treat patients were less than 10%, and the SVR rates in low viral load (less than 100 KIU/mL) or genotype 2a/2b patients were 50 to 70%. Many studies including the present one have reported alternative treatments involving the addition of other agents or different IFN doses within 6 months.[11–13] The SVR rate in our study was similar to those obtained in previous studies.

CIFN was developed through recombinant technology and was expected to be more effective than other agents for chronic hepatitis C. Several reports demonstrated greater efficacy of CIFN as compared with other types of IFN, such as natural IFN (7), IFN-α2a or α2b.[14] It

appears that the frequency of adverse reactions with CIFN is less than that with other IFNs, so CIFN can be used at a higher dose in patients with chronic hepatitis C.[15,16] The standard dose of CIFN was set at 18 MU/day, a dose which is not tolerable with other types of IFN. Sjögren *et al*.[17] demonstrated that the combination of CIFN and RBV provided better response compared with the combination of IFN-α2b and RBV in patients infected with genotype 1 and a high viral load. In the present study, 18 MU/day of CIFN was also well tolerated and induction therapy with twice-daily IFN-β tended to be less tolerable. No significant reason other than a bias of aged patients has been found why the number of dropped out patients in group II was larger than that in group I.

Induction therapy with daily CIFN until the disappearance of HCV RNA was reported to be effective in eliminating HCV RNA at 12 weeks but the final SVR rate was not superior to treatment without induction therapy. Induction therapy always decreases serum HCV RNA more rapidly than does ordinal therapy, however Layden and colleagues[18] reported that induction therapy with CIFN did not increase SVR rates as compared with therapy without induction. Zeuzem[19] suggested the likelihood that SVR rates would be increased by induction therapy for more than 2 weeks, however Pockros[20] demonstrated that daily dosing of CIFN might be difficult to tolerate, resulting in discontinuation of therapy in a significant proportion of patients. These results suggest that induction therapy with CIFN is not effective in increasing response rates. Hirashima and associates[21] used a combination of lactoferrin with CIFN therapy, and found no additive effect. However, Zeuzem,[19] still recommended additional induction-type studies focused on naïve difficult-to-treat patients and on previous non-responders, even after the introduction of Peg-IFN. We investigated the effect of induction therapy with twice-daily IFN-β on CIFN treatment in this study.

Induction therapy with twice-daily IFN-β has been shown to improve the efficacy of IFN-α monotherapy,[22–24] although response rates for patients with both genotype 1b and a high titer of HCV RNA were low. Although Suzuki and colleagues [25] reported that twice-daily administration was not superior to a once-daily regimen for patients with genotype 1b and high HCV RNA levels, twice-daily therapy did changes HCV dynamics in the early phase of IFN-α monotherapy [26] and IFN-α2b plus RBV combination therapy.[8] We compared CIFN monotherapy regimens with and without induction therapy with twice-daily IFN-β. SVR rates of the induction therapy group were similar with those of CIFN monotherapy group, and no beneficial effect of the induction therapy was found even in patients with genotype 2a/2b. Therefore, the results of this study lead us to conclude that induction therapy with IFN-β did not improve the therapeutic efficacy of CIFN monotherapy for chronic hepatitis C.

Normalization of serum transaminase levels is a good prognostic factor in patients with chronic hepatitis C, but induction therapy did not always decrease transaminase levels in this study. After cessation of therapy, serum transaminase levels normalized in the same proportion of patients in both treatment groups, since SBR rates of the groups were similar. The levels during treatment, however, were always higher in patients of group II than in those of group I, indicating that induction therapy was not superior for stabilizing hepatic injury. The elevation of serum ALT levels during IFN-β therapy has been reported previously and did not seem to result from increased hepatitis activity,[27] but the elevation of transaminase levels during treatment may have no beneficial effect on liver function, if good biochemical and virological responses could be obtained thereafter.

There are some limitations to this study. One is that the mean age of patients in the induction group was significantly older than that of patients without induction therapy, even though the patients were randomly assigned. This confounding due to age for the induction group was one of reasons why the IFN-β induction was not effective in this study. Failure of randomization and higher truncation of treatment during the treatment period could lead to underestimation of efficacy of the IFN-β induction therapy. On the contrary, CIFN exerts strong antiviral effect on HCV infection, and daily CIFN administration showed similar antiviral effect with twice-daily IFN-β administration as for negative rate for HCV at the first 2 weeks. In this study, negative rate at the first 4 weeks was 85.7% and 63.6% (p=NS) in CIFN group and IFN-β induction group, respectively. Therefore, it is also considered that antiviral effect of the IFN-β induction does not superior to the daily CIFN administration. There must be enough number of subjects to avoid having larger random variation of outcome indices. However, the number of patients enrolled in this trial was small. Enrollment of many more patients might have overcome this limitation, but we found it difficult to recruit additional patients, since the use of RBV was approved at the same time with this study, and IFN-α 2b plus RBV combination therapy was indicated for the same group of patients participating in this study. It was already known that IFN-α2b plus RBV combination therapy achieves much more SVR rates than IFN-monotherapy even the induction therapy was introduced. Therefore, patients with chronic hepatitis C easily refused our offer to participate in this study at that time. In conclusion, our results suggest that induction therapy with twice-daily IFN–β is not much superior to the therapeutic efficacy of CIFN monotherapy, and a large study may clarify whether the induction therapy improves efficacy.

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